

Claims

1. (original) A heterologous fusion protein comprising a GLP-1 analog comprising a sequence selected from the group consisting of:
 - a) (SEQ ID NO:1)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly
wherein Xaa₈ is selected from Gly and Val;
 - b) (SEQ ID NO:2)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly
wherein Xaa₈ is selected from Gly and Val;
 - c) (SEQ ID NO:3)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro
wherein Xaa₈ is selected from Gly and Val;
 - d) (SEQ ID NO:4)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro
wherein Xaa₈ is selected from Gly and Val;
 - e) (SEQ ID NO:5)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly
wherein Xaa₈ is selected from Gly and Val;
 - f) (SEQ ID NO:6)
His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly
wherein Xaa₈ is selected from Gly and Val;
fused to the Fc portion of an immunoglobulin comprising the sequence of
SEQ ID NO:7
Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-
Xaa₁₆-Xaa₁₇-Xaa₁₈-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-
Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-
Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-
Glu-Glu-Gln-Phe-Xaa₈₀-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-

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Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Leu-Gly-Xaa₂₃₀ (SEQ ID NO:7)

wherein:

Xaa at position 16 is Pro or Glu;

Xaa at position 17 is Phe, Val, or Ala;

Xaa at position 18 is Leu, Glu, or Ala;

Xaa at position 80 is Asn or Ala; and

Xaa at position 230 is Lys or is absent.

2. (original) The heterologous fusion protein of Claim 1 wherein the C-terminal glycine residue of the GLP-1 analog is fused to the N-terminal alanine residue of the Fc portion via a peptide linker comprising a sequence selected from the group consisting of:
 - a) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Ser (SEQ ID NO:8);
 - b) Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:19); and
 - c) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:21).
3. (original) The heterologous fusion protein of Claim 2 wherein the linker comprises the sequence of SEQ ID NO:8.
4. (original) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Gly.
5. (original) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Val.
6. (original) The heterologous fusion protein of any one of Claims 1 to 3 wherein the GLP-1 analog comprises the sequence of SEQ ID NO:1.
7. (original) A heterologous fusion protein selected from the group consisting of: a) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P); b) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4

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- (S228P, N297A); d) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P); j) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
8. (original) A heterologous fusion protein selected from the group consisting of: a) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P); b) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P); j) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
- 9.-15. (cancelled)
16. (original) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.
17. (original) A method of inducing weight loss in an overweight patient comprising the administrations of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.
18. (original) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered at a dose between about 0.05 mg/kg to 0.5 mg/kg body weight.
19. (original) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered once a week.
- 20.-24. (cancelled)
25. (new) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous

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fusion protein of any one of Claims 1 to 8, wherein the fusion protein stimulates insulin secretion, inhibits glucagon secretion, inhibits gastric emptying, inhibits gastric or intestinal motility, or induces weight loss.